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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,635	11/12/2003	Richard W. Moyer	UF-221C1XCZ1	8304

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/706,635	MOYER ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/15/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-16 are pending and under examination in the instant application. An action on the merits follows.

Please note that any declarations or supporting evidence provided in the parent applications must be resubmitted in the instant application in order to be considered.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, and 8-15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14-21 of U.S. Patent No.6,106,825, 8/22/00, hereafter referred to the '825 patent. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons. The claims of

the '825 patent are both broader and narrower than the instant claims. The '825 claims recite methods for delivering a heterologous gene to a vertebrate cell comprising contacting the cell with a recombinant entomopox virus (rEPV) encoding a heterologous gene operatively linked to a early vaccinia virus promoter, wherein the contacting occurs in vitro or in vivo. Instant claim 1 recites methods for delivering a polynucleotide encoding a protein to a vertebrate cell comprising introducing into the cell an rEPV comprising the polynucleotide encoding the protein operably linked to a promoter sequence. Claim 14 recites a vertebrate cell comprising an rEPV comprising a polynucleotide encoding a protein operably linked to a heterologous promoter sequence. Thus, the '825 claims represent a species of the instant claims in that an early vaccinia virus promoter is a species of promoter sequences and further a species of a heterologous promoter. It is well established that a species of a claimed invention renders the genus obvious. In re Schaumann , 572 F.2d 312, 197 USPQ 5 (CCPA 1978).

The '825 claims are also broader than the instant claims in that they do not specifically recite the limitations of instant claims 2-6, 8-13, and 14-15. However, these limitations are clearly taught as preferred embodiments of the methods claimed in the '825 patent in columns 7-9, 14-15, and 16. Thus, by specifically claiming the same methods as the instant claims, and by teaching all of the specific limitations recited by the instant claims, the claims of the '825 patent render claims 1-6, and 8-15 obvious.

Claims 1-10, and 12-16 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 and 21 of U.S. Patent No. 6,127,172 (10/3/00), hereafter referred to as the '172 patent. Although the conflicting claims are

not identical, they are not patentably distinct from each other for the following reasons. The patented claims recite the exact same subject matter as instant claims 1-10 and 12-15 except that the patented claims are narrower than the instant claims in that the patented claims are restricted to the use of a heterologous early promoter sequence whereas the instant claims do not recite a specific promoter except for claim 7 which recites the same species of promoters as claim 6 of the '172 patent. It is well established that a species of a claimed invention renders the genus obvious. In re Schaumann , 572 F.2d 312, 197 USPQ 5 (CCPA 1978). Thus, the patented claims render the instant claims 1-10 and 12-15 obvious.

In regards to claim 16 which is limited to a human cell and non-pox virus promoters, claim 21 of the '172 patent encompasses these limitations by reciting a vertebrate cell and an early promoter sequence. Further, these limitations are clearly taught as preferred embodiments of the invention in the '172 patent in column 6, claims 3 and 6. Thus, by specifically claiming the same methods and cells as the instant claims, and by teaching all of the specific limitations recited by the instant claims, the claims of the '172 patent render claims 1-10 and 12-16 obvious.

Claims 1-10, and 12-16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 76-85, 88-89, and 101-102 of copending Application No. 09/662,254, hereafter referred to as the '254 application. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. The claims in the '254 application are a species of instant claims 1-10 and 12-15 in that claims in the '254 application are limited to heterologous early poxvirus promoters or non-poxvirus promoters whereas the instant claims broadly read on promoters or

heterologous promoters. It is well established that a species of a claimed invention renders the genus obvious. In re Schaumann , 572 F.2d 312, 197 USPQ 5 (CCPA 1978). Thus, the patented claims render the instant claims 1-10 and 12-15 obvious.

In regards to claim 16 which is limited to a human cell, claims 101-102 of the '254 application encompass this limitations by reciting a vertebrate cell. Further, this limitation is clearly taught as a preferred embodiment of the invention in the '254 application, see for instance claim 78. Thus, by specifically claiming the same methods and cells as the instant claims, and by teaching all of the specific limitations recited by the instant claims, the claims of the '254 application render claims 1-10 and 12-16 obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. However, please note that these claims have been allowed and publication is pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant entomopox virus vector comprising a heterologous polynucleotide encoding a gene under transcriptional control of a promoter with early gene

transcriptional activity, a viral particle comprising said vector, an isolated cell infected or transfected *in vitro* with said recombinant virus or vector wherein the protein encoded by said heterologous polynucleotide is expressed in the cell, and a method of *in vitro* delivery of a gene to a cell comprising infecting or transfecting cells with said recombinant virus or vector, does not reasonably provide enablement for entomopox vectors and viruses capable of expressing therapeutically effective amounts of a protein either *in vitro* or *in vivo*, or for a method for providing a vertebrate animal with a therapeutically effective amount of a protein encoded by said entomopox viruses and vectors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The applicant's specification discloses recombinant entomopox virus vectors useful for generating recombinant entomopox virus particles which can then be used to infect vertebrate cells resulting in expression of a heterologous gene product encoded by the entomopox virus. The specification further discloses that said recombinant entomopox viral DNA or viral particles can be used to infect, transfect, or transduce an animal wherein the expression of therapeutic amounts of the heterologous protein in the animal results in the amelioration of diseases or conditions caused by protein deficiencies or abnormalities. As a preferred embodiment, the specification discloses that proteins such as interleukins, cytokines, enzymes, structural proteins, growth hormones and interferons can be expressed in a vertebrate animal using the recombinant entomopox viruses of the instant invention, wherein the amount of protein expressed is of therapeutic benefit to the animal (specification, pages 6 and 12).

The specification provides working examples demonstrating the construction of recombinant entomopox vectors with a heterologous polynucleotide encoding green fluorescent protein (GFP) under control of the CMV promoter or the *esp* promoter inserted into the EPV thymidine kinase gene, and the production of recombinant entomopox viral particles using said vectors. The specification further discloses that vertebrate CV-1 and 293 cells can be infected *in vitro* with the recombinant entomopox resulting in detectable levels of GFP expression. The specification further demonstrates the intramuscular injection of a recombinant entomopox encoding lacZ under control of the *esp* promoter into mice resulting in the detectable expression of lacZ in the muscle on day 2.

The specification does not provide an enabling disclosure for the use of any promoter sequence to control transcription of a therapeutic or marker gene in mammalian cells infected or transfected with recombinant entomopox vectors of the instant invention. The specification discloses that entomopox cannot productively infect mammalian cells and that gene expression is limited to early promoter activity (specification, pages 13-14, bridging paragraph). Specifically, the specification discloses that late poxvirus promoters such as AmEPV spheroidin or cowpox virus ATI are inactive in mammalian cells infected with recombinant EPV. In view of this requirement for the use of promoters with early gene transcription activity, the skilled artisan would not predict that any and all promoter sequences could express a heterologous gene of interest when encoded by a recombinant entomopox virus.

The specification does not provide an enabling disclosure for the *in vivo* delivery of therapeutically effective recombinant entomopox viruses or vectors to animals. The specification discloses that the entomopox virus vectors or particles can be delivered to the animal by direct

injection or transfection, or by *ex vivo* infection or transfection of isolated cells followed by administration of the recombinant cells to the animal. The specification provides a single working example demonstrating *in vivo* delivery of any recombinant entomopox virus by intramuscular injection to mice resulting in *in vivo* expression of the virally encoded protein in the muscle. However, the example only examines expression of day two following injection and does not correlate the level or duration of gene expression with any therapeutic effect on any disease or condition. The specification provides no guidance as to other routes or sites of injection, or provides guidance as to the dosage of virus or cells comprising viral vector capable of leading to expression of therapeutic levels of heterologous gene expression *in vivo*. In addition, the specification does not disclose what constitutes a therapeutically effective amount of protein expression, or disclose the duration and location of protein expression necessary for amelioration or treatment of any and all disorders. The specification's description of the disorders to be treated using the applicant's entomopox viruses reads on all genetic disorders (e.g. ADA deficiency, sickle cell anemia, hypergammaglobulinemia, Huntington's disease) and cancer. The applicant's own publication teaches that recombinant entomopox viruses exhibit biased gene expression in different vertebrate cell types. Li et al. disclose that in an experiment involving the *in vitro* infection of a panel of vertebrate cell lines with a recombinant entomopox virus encoding LacZ, infected hepatocytes and fibroblasts expressed significantly higher levels of β-galactosidase compared to lymphoid cells, which showed little to no expression (Li et al. (1997) J. Virol., Vol. 71 (12), page 9560, Figure 4, and page 9562, paragraph 2). Thus, the skilled artisan would not predict that the entomopox viruses of the instant invention could be used to

express therapeutic levels of protein in lymphoid cells associated with disorders such as ADA deficiency, Burkitt's's lymphoma, or ataxia telangiectasia.

Furthermore, the art at the time of filing did not consider gene therapy of genetic diseases or cancer using recombinant vectors as predictable. Verma et al. identified the "Achilles heel" of gene therapy as gene delivery, and states that , ".. the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (Verma et al. (1997) Nature, Vol. 389, page 239, column 3, paragraph 2). In regards to viral vectors, Verma et al. teach that host immune responses can result in transient gene expression and prevent subsequent revaccination, which will be required for gene therapy of diseases involving differentiated cells due to high cell turnover (Verma et al., *supra*, page 239, column 3, paragraph 3, page 241, column 1, paragraph, 4, and page 242, column 3, paragraph 2). Li et al. disclose that active gene expression ceases at approximately 24 hours post infection of vertebrate cells with entomopox virus encoding GFP, and that cell division of the infected cells results in diminished fluorescence as the GFP is distributed between daughter cells (Li et al., *supra*, page 9560-9561, column 3, paragraph 3-paragraph 1). Further, the specification does not provide guidance as to the dosage or routes of delivery of entomopox virus to a mammal that has already received a first injection.

In addition, Orkin et al. states that, " while the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol", and that , " none of the available vector systems is entirely satisfactory , and many of the perceived advantages of vector systems have not been experimentally validated" (Orkin et al. (1995) "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy"). Ross et al. in a review of current gene therapy protocols concurs,

concluding that, " it is clearly too early.. to assess the therapeutic efficacy of gene therapy or even to predict its promise" (Ross et al. (1996) Human Gene Therapy, Vol. 7, page 1789, paragraph 2). Marshall concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1). Therefore, in view of the quantity of experimentation necessary to determine the parameters affecting gene delivery, particularly viral dosage and the site and routes of administration, the lack of direction or guidance provided by the specification concerning these and other issues listed above, the absence of working examples for *in situ* gene therapy, the breadth of the claims, and the unpredictable and undeveloped state of the art with respect to *in vivo* gene therapy, one skilled in the art at the time of filing would not have had a reasonable expectation of success in delivering a therapeutically effective amount of a protein to a vertebrate animal using the entomopox virus and vectors of the instant invention.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the

technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER